University of Maryland, Baltimore
Tenth Annual Women's Health Research Symposium
Sex and Rx: A Symposium on Women and Medications
Baltimore, MD October 24, 2003

Gender Differences in Drug Response-Metabolism and Transport Differences: How Much Do We Know?

Shiew-Mei Huang, Ph.D.
Deputy Office Director for Science
Office of Clinical Pharmacology & Biopharmaceutics, OPS
CDER, FDA

FDA's Strategic Action Plan

Improving patient and consumer safety

- **Reducing risks**
- **Understanding risks in specific populations**
- **DailyMed project**

Improving health care through better information

- **ensure that information by a product's sponsor is accurate**
- **….**

< FDA Commissioner, McClellan, MB, FDA Strategic Action Plan; August 2003>
<http://http://www.fda.gov/oc/mcclellan/strategic.html>

Adverse Drug Reactions

- Account for 5% of hospital admissions
- Experienced by 10% of hospitalized patients
- Result in 700,000 injuries/deaths per year
- Either the 4th or 6th leading cause of death
- 51% of drugs cause serious ADRs that aren't detected until they're on the market

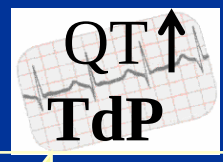
Einarson T, Ann. of Pharmacotherapy,1993;27:832-839
Bates, DW, et al, JAMA 1997; 277:307-11
Lazarus J et al, J.Amer.Med.Assoc. 1998;270:1200-1205

Post-marketing dosage changes 1980-1999 (n= 499)

- 71% evaluable
- 21% had dosage changes
- 79% safety-related reduction
- changes included: specific populations and drug interaction sections

Cross J, et al, Pharmacoepidemiology Drug Safety, September, 2002

Recent US Market Withdrawal/NA -Examples



Hepato-tox

Others

1998	Terfenadine Mibefradil Bromfenac
1999	Astemizole Grepafloxacin Drug X (NA)
2000	Troglitazone Cisapride Alosetron*
2001	Cerivastatin Papacuronium Drug Y (NA)

* reintroduced in 2002

Elderly populations

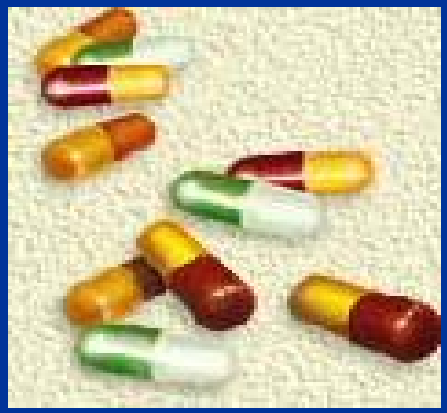
- **... Patients ..with ACE inhibitors .. with .. hyperkalemia (n = 523) were ~ 20 times more likely to have a... potassium-sparing diuretic in the previous week**

- **...Patients .with digoxin toxicity (n = 1051) were about 12 times more likely to have ... clarithromycin in the previous week...**

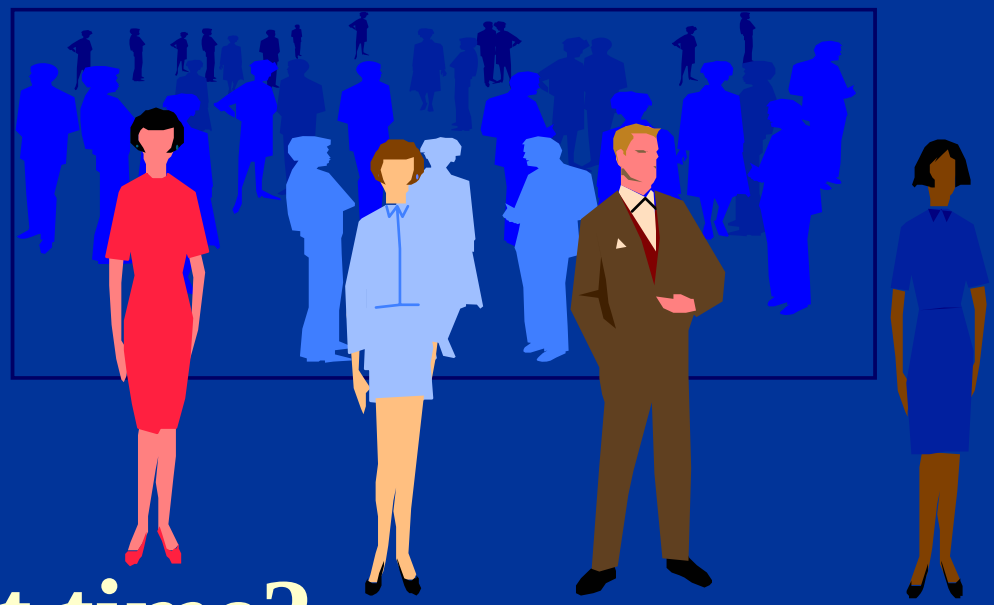
<JAMA, 2003;289 (13):1652 >

Clinical Pharmacology & Biopharmaceutics:

Right drug?



Right patient?



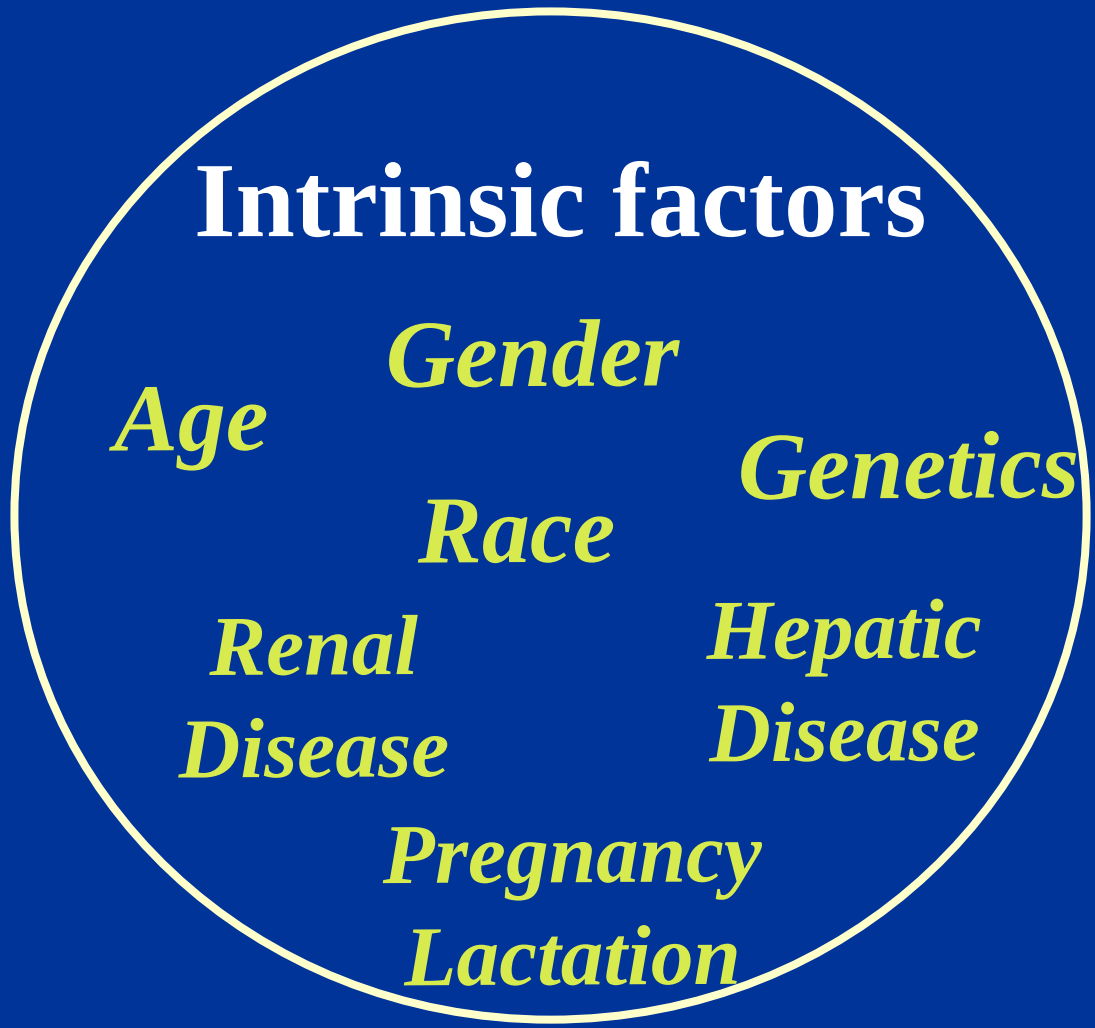
Right time?

Right dose/dosage form?

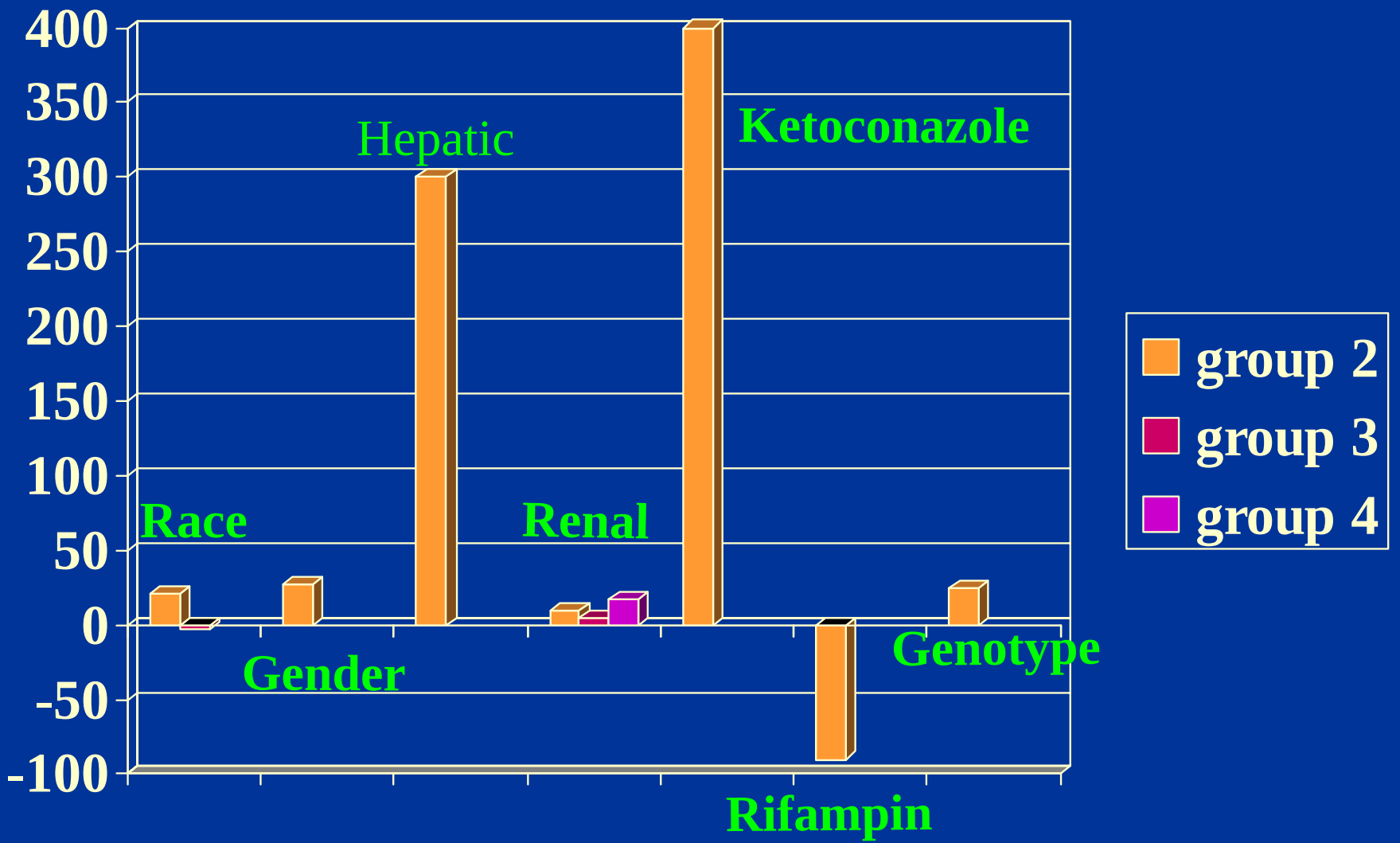

FINAL
FINAL

Extrinsic factors

Drug-drug interaction **Smoking/Diet**



% Change in Exposure (AUC or Cmax)



Group 1: control

Tacrolimus Labeling

- ***Dosage and Administration***

  The data in kidney transplant patients indicate that the *Black patients* required a higher dose to attain comparable trough concentrations compared to Caucasian patients.

  ***Pediatric* liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations**

Rosuvastatin Labeling

- *Precautions- General*

Pharmacokinetic studies show.. 2-fold elevation in median exposure in *Japanese subjects residing in Japan* and in *Chinese subjects residing in Singapore* compared with Caucasians residing in North America and Europe….. these increases should be considered … dosing decisions for ..Japanese and Chinese ancestry (see WARNINGs Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race).

Montelukast Labeling

- ***Adolescents and Pediatric Patients:***

  10-mg in patients >/=15 years of age.
  5-mg in 6 to 14 years of age;
  4-mg in 2 to 5 years of age.

- ***Gender:*** **The pharmacokinetics …similar in males and females.**

- ***Elderly/Renal Insufficiency :*** **No dosage adjustment is required.**

Pioglitazone Labeling

- *Clinical Pharmacology*

  The mean Cmax and AUC values were increased 20 to 60% in females

  In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%).

Sertraline Labeling

- ***Major Depressive Disorder***
- **Obsessive-Compulsive Disorder (OCD)**
- ***Panic Disorder*** **……**

Analyses for gender effects on outcome did *not* suggest any differential responsiveness on the basis of sex

- **Posttraumatic Stress Disorder (PTSD)**

Post hoc exploratory analyses revealed a *significant* difference between ZOLOFT and placebo on the CAPS, IES and CGI *in women*, regardless of baseline diagnosis of comorbid major depressive disorder, but essentially *no effect* in the relatively smaller number of *men* in these studies.

Simvastatin Labeling

- ***Drug Interactions :*** **Potent inhibitors of CYP3A4 may increase the risk of myopathy …. cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (>1 quart daily)…... should be avoided.**

- ***Nursing Mothers*****: women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS)**

Atomoxetine Labeling

• ***Clinical Pharmacology:*** **Poor metabolizers (PM) of CYP2D6…... 10-fold higher AUC**

• ***Drug-Drug Interactions:*** **Dosage adjustment ...in EMs ….. ... with CYP2D6 inhibitors, eg, paroxetine, fluoxetine, and quinidine …... In vitro studies suggest that ….. P450 inhibitors to PMs will <u>not</u> increase the plasma concentrations of atomoxetine**

• ***Laboratory Tests :*** **Laboratory tests are available to identify CYP2D6 PMs …….*higher blood levels in PMs lead to higher rate of some adverse effects of STRATTERA*.**

FR Notice 1998

Final Rule on Investigational New Drug Applications and New Drug Applications

(21 CFR Parts 312 and 314)

- ***requires that analyses of effectiveness and safety data for important demographic be submitted to NDAs.***

- ***enrollment of subjects …… be tabulated by important demographic subgroups in IND annual reports, i.e., age group, gender, and race.***

- ***This final rule allows the Agency to refuse to file any NDA that does not analyze safety and efficacy information appropriately by subgroups.***

1993 Guidance

Guideline for the Study and Evaluation of Gender Differences in Clinical Evaluation of Drugs

• *there are many quantitative differences, ..in dose-response, maximum size of effect, or in the risk of an adverse effect. ..., sponsors are expected to …... carry out appropriate analyses to evaluate potential subset differences, study possible pharmacokinetic differences in patient subsets, and .. targeted studies to look for subset pharmacodynamic differences ….*

Comparative ADR reports (withdrawn drugs)

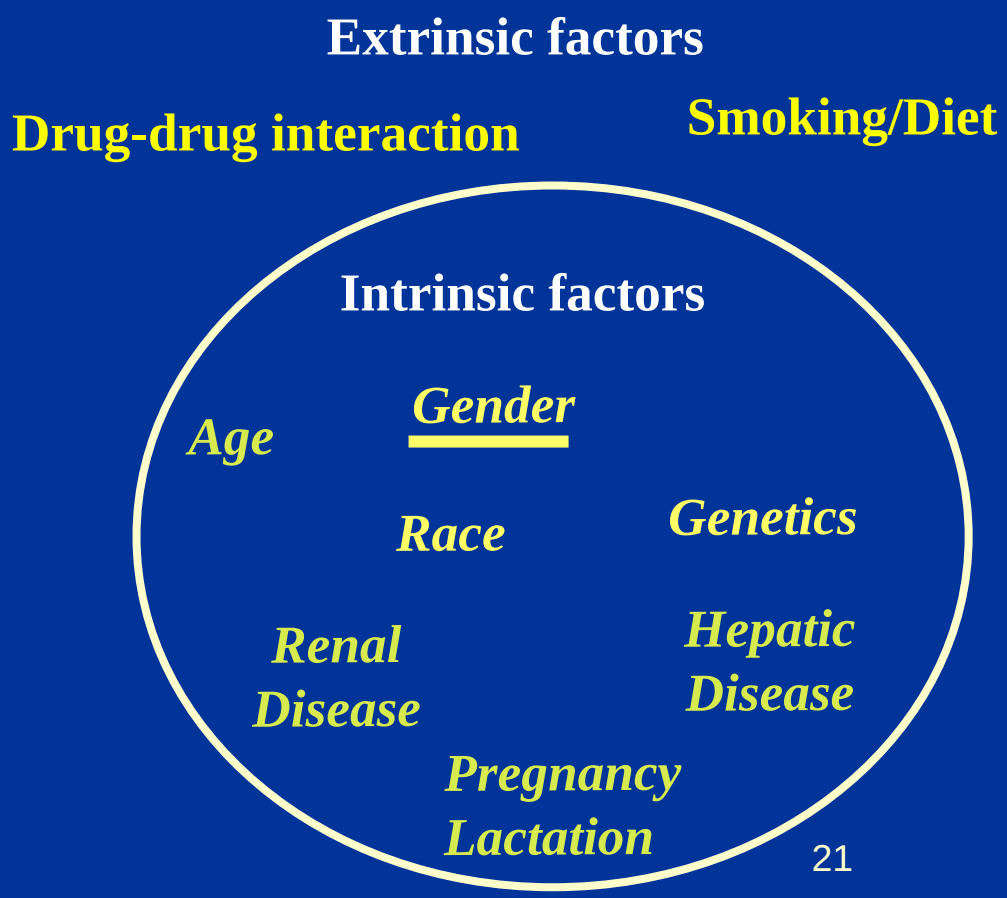
Year	Drugs	Use	F/M (1)	F/M (2)
1998	Mibefradil	47/52	61/22	70/21
	Terfenadine	61/33	72/28	68/20
	Bromfenac	56/41	58/42	
1999	Astemizole	63/32	55/23	93/7
	Grepafloxacin	51/44	54/38	----**
2000	Alosetron	86/10	99/1	
	Cisapride	57/40	61/37	66/34
	Troglitazone	53/42	65/35	

***Use data from IMS database; F/M for all ADR (1); TdP/QT prolongation only (2)**

< Huang SM, Miller M, Toigo T, Chen MC, Sahajwalla C, Lesko L,Temple R, Evaluation of Drugs in Women: Regulatory Perspective– in Section **11, Drug Metabolism/Clinical Pharmacology (section editor: Schwartz, J), in "Principles of Gender-Specific Medicine", Ed., Legato M, Academic Press (in press) >**

Basis for these differences

- ***Pharmacokinetic***
- ***Pharmacodynamic***



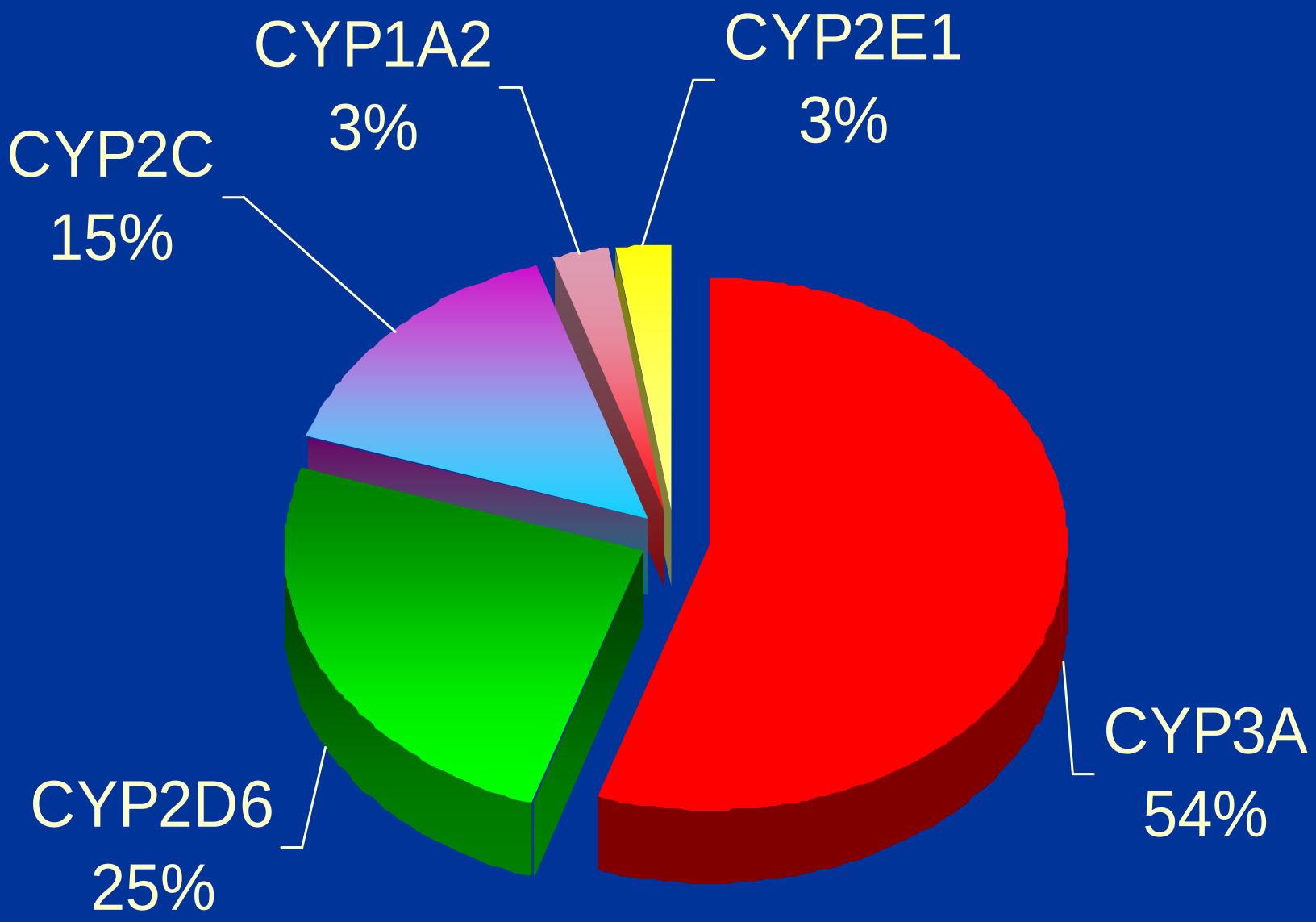
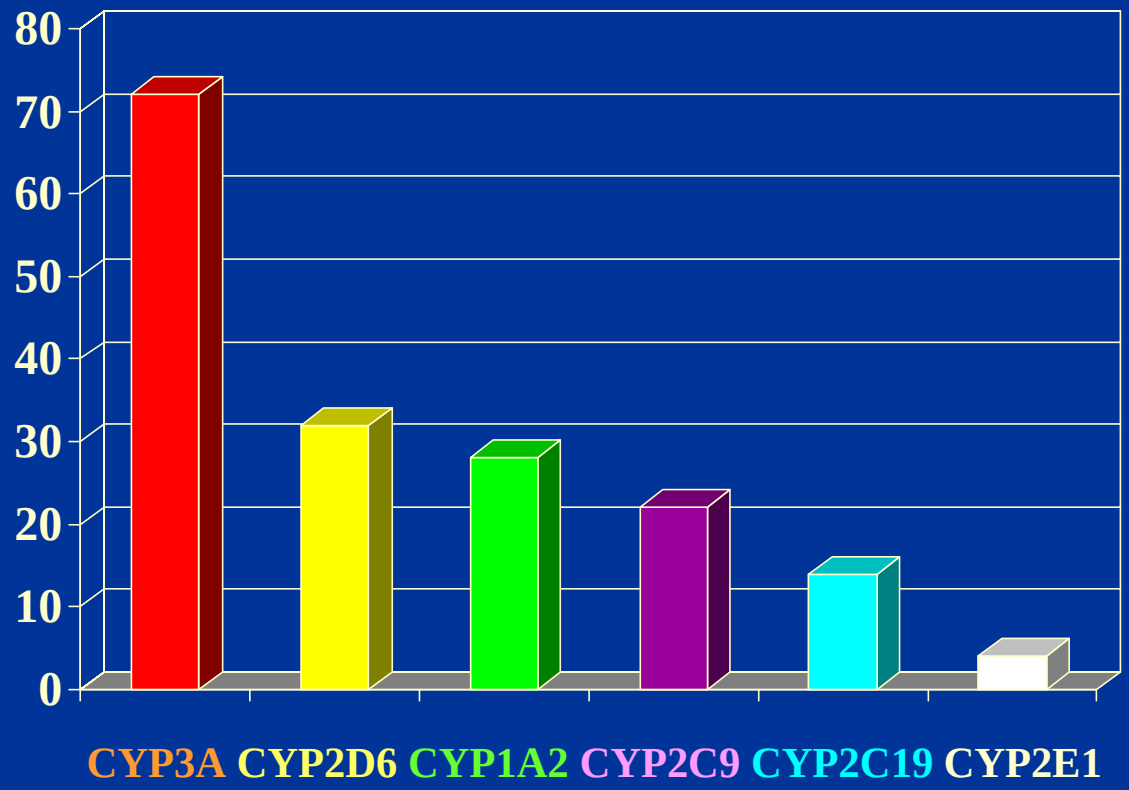

CYP1A2
3%
CYP2E1
3%
CYP2C
15%
CYP3A
54%
CYP2D6
25%

Figure 1. Number of drugs metabolized by CYP enzyme (data from 163 NDA submitted between 1994 and 2000).

-- Note that many drugs are substrates of multiple enzymes, in addition to transferases and transporters

Levels

F=M 45
F>M 22
M>F 5



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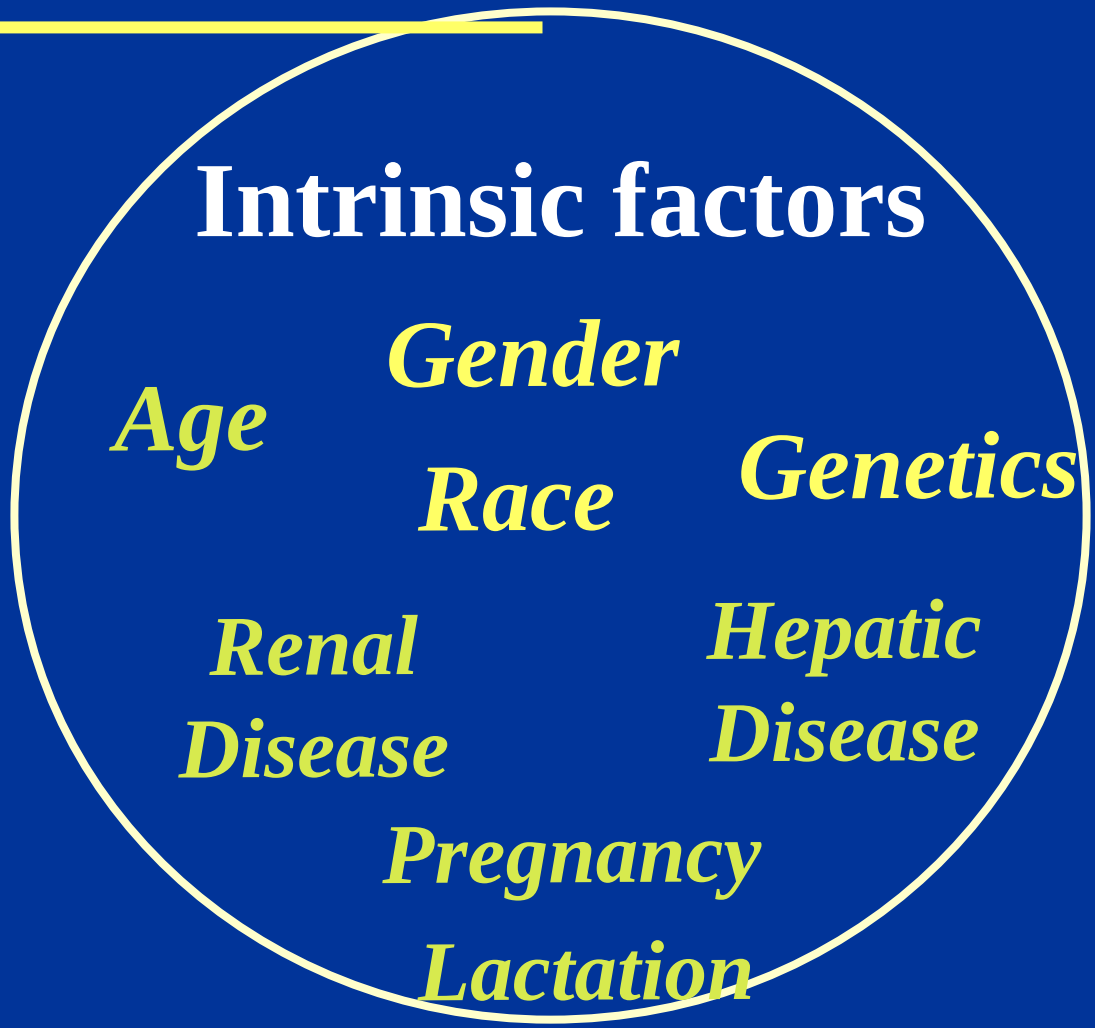
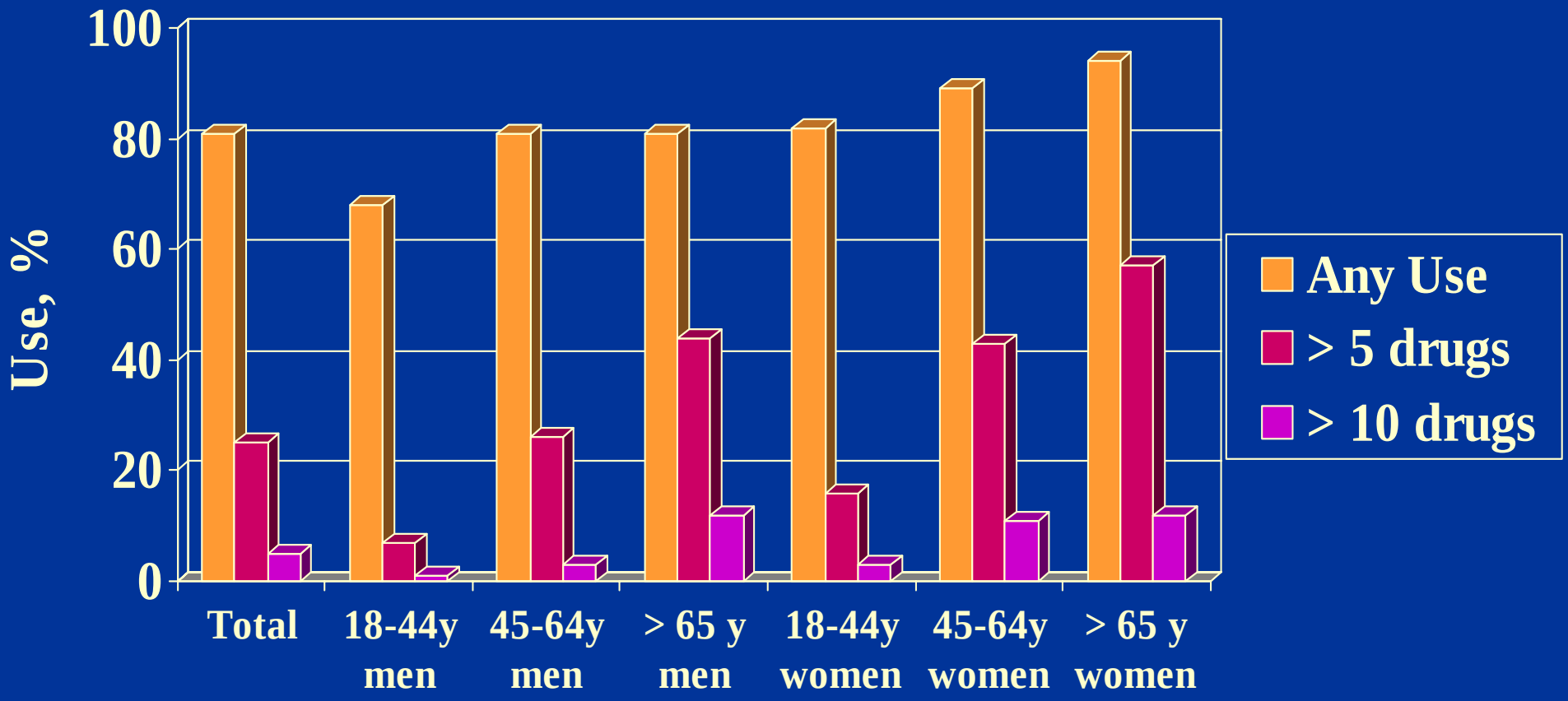
Extrinsic factors

Drug-drug interaction **Smoking/Diet**

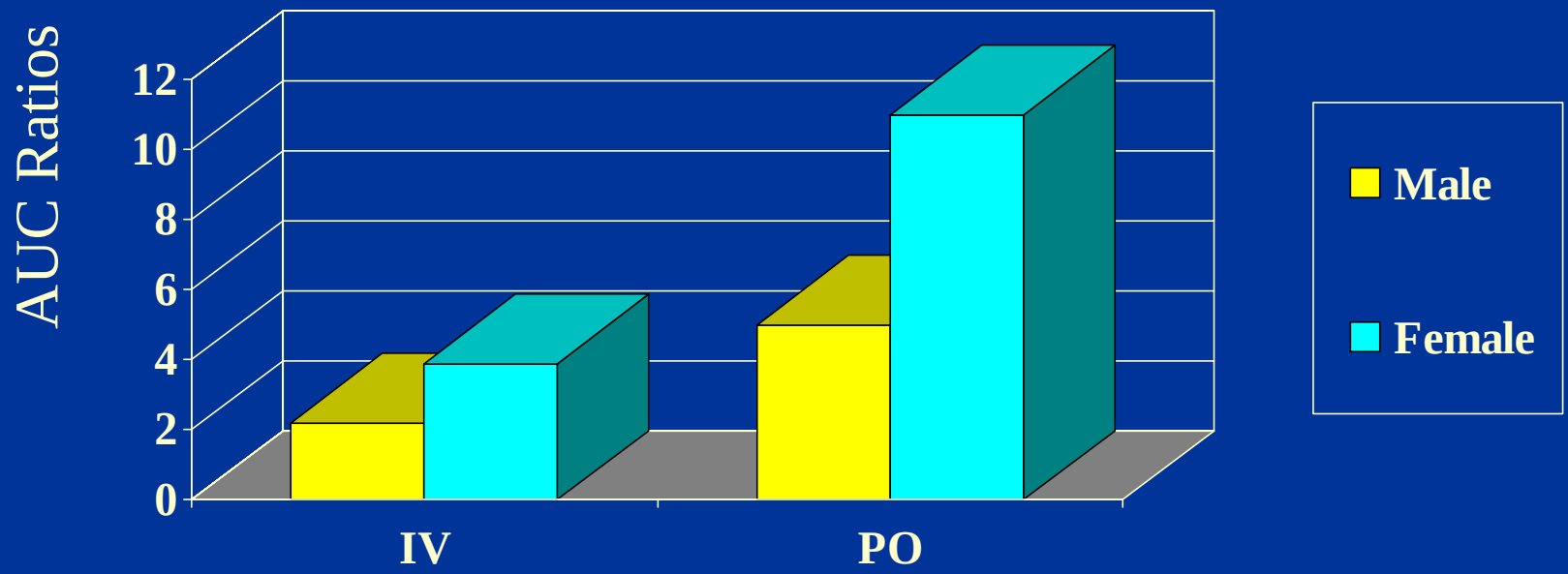


Use of Medications by Sex and Age



< JAMA 2002;287:337-344 >

Gender Differences in Extent of Interactions - Clarithromycin on midazolam.



<Data from Gorski JC et al., Clin Pharmacol Ther 64: 133-143, 1998>

St John's Wort interactions

- 8 weeks of St John's Wort *decreased* norethindrone levels and ethinyl estradiol t1/2

- More breakthrough bleeding occurred in St John's Wort phase

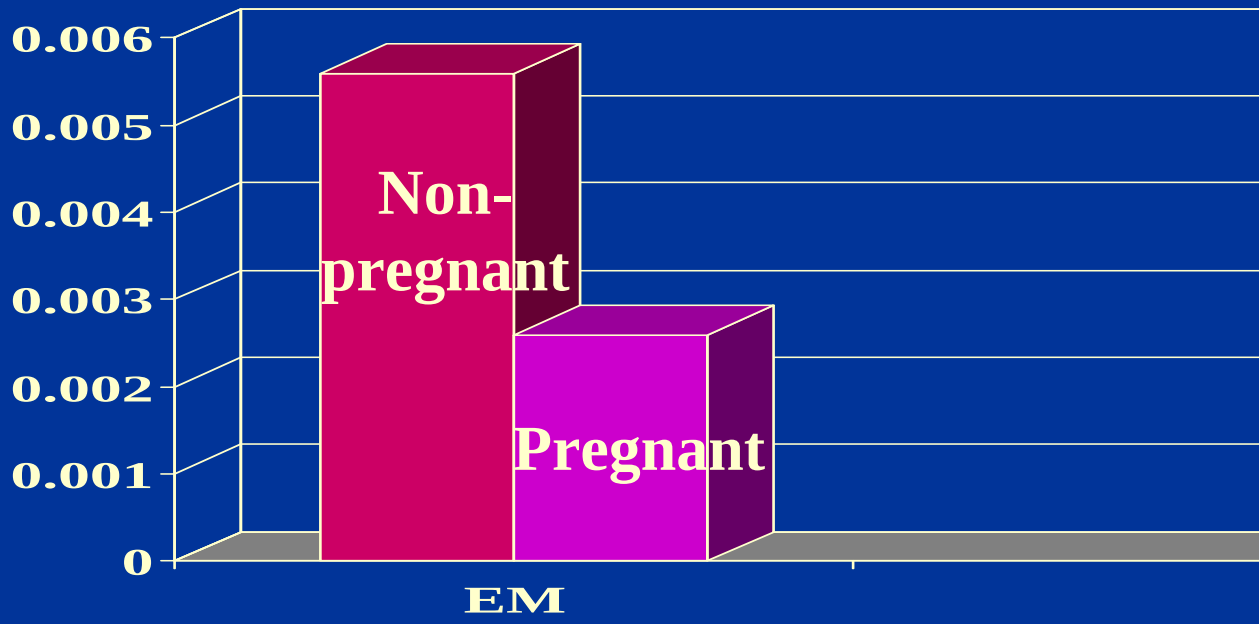
- Higher midazolam clearance for those with breakthrough bleeding

  (216+ 67 vs. 98 +37)

< Gorski C, et al, FDA Science Forum, April 2003>

Literature on various CYPs in Pregnancy

CYP2D6



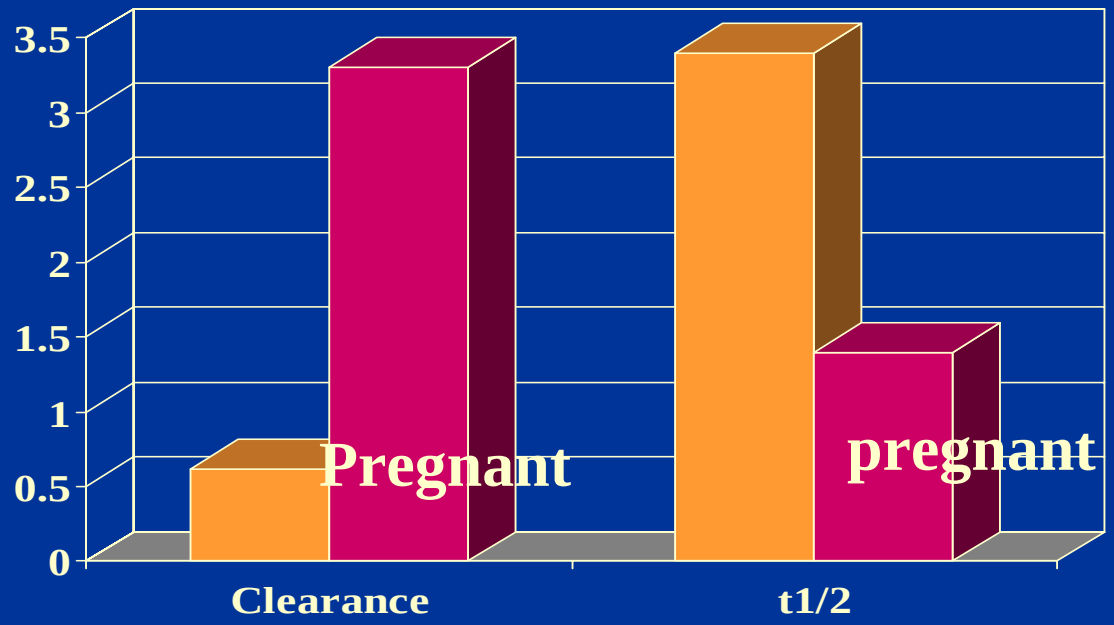
- Dextromethorphan/dextrorphan metabolic ratio

- 36 wk vs. 7-11 wk postpartum (healthy; n=13 EM; n=4 PM)

- EM: homozygous and heterozygous extensive metabolizers; PM: *3, *4

< Wadelius M, et al, Clin Pharmacol Ther 1997>

CYP3A



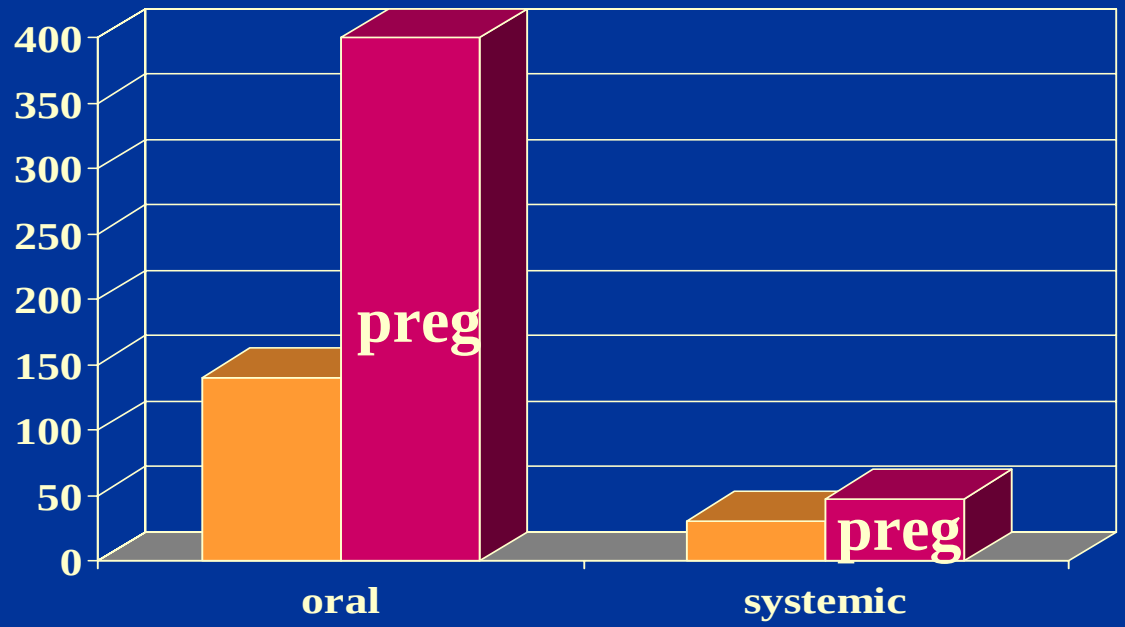
- nifedipine (oral)

- immediately post-partum preeclampsia (n=8) vs. or normotensive non-pregnant volunteers (n=12)

- cross study comparison < 5-fold>

< Barton JR, et al, Am J Obstet Gynecol 1991; Foster TS, et al, J Clin Pharmacol 1983>

CYP3A



- midazolam (oral and IV)
- 38-41 wk (n=8) vs. non-pregnant (n=16)
- cross study comparison <3-fold oral Cl>

< Gorski JC et al, Clin Pharmacol Ther 1998; Kanto J et al, Clin Pharmacol Ther 1983>

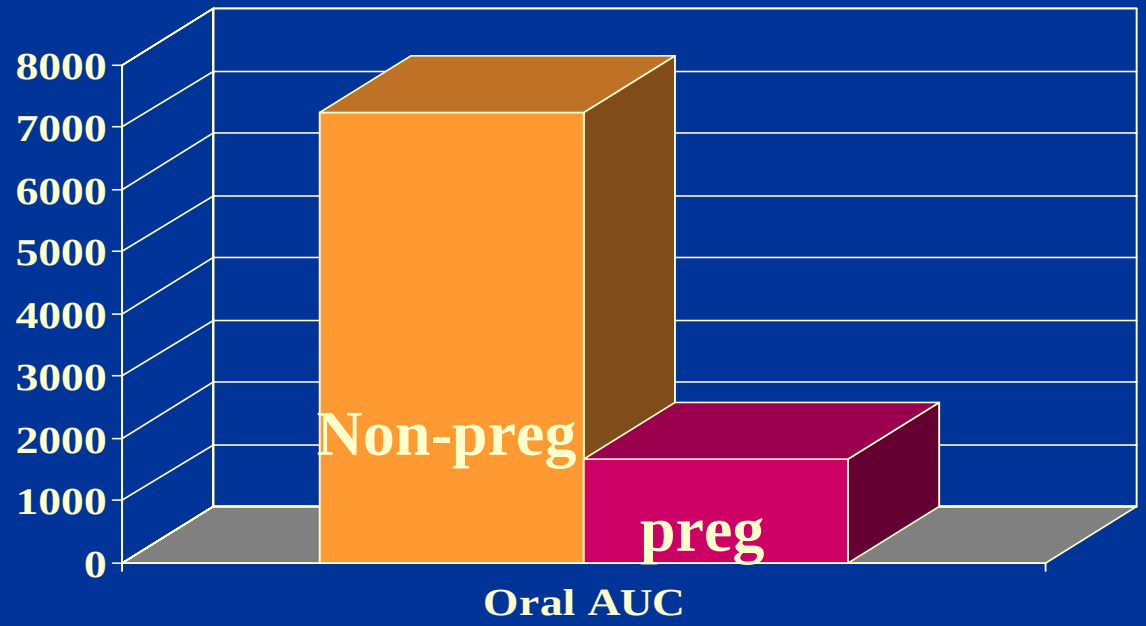
P-gp substrates

Aldosterone
Amprenavir
Bilirubin
Cimetidine
Colchicine
Cortisol
CPT-11 (Irinotecan)
Cyclosporine
Dexamethasone
Digoxin
Diltiazem
Domeperidone
Doxorubicin
Erythromycin
Estradiol-17B-D-glucuronide
Etoposide
Fexofenadine

Indinavir
Itraconazole
Ivermectin
Loperamide
Methylprednisolone
Morphine
Nelfinavir
Paclitaxel
Quinidine
Ranitidine
Rhodamine
Saquinavir
Sparfloxacin
Terfenadine
Tetracycline
Vecuronium
Verapamil
Vinblastine

< Kim RB, Drug Metab. Rev. 34,47 (2002)>

Saquinavir



- saquinavir (1200 mg tid) with lamivudine 150 mg bid & zidovudine 200 mg tid; n=10

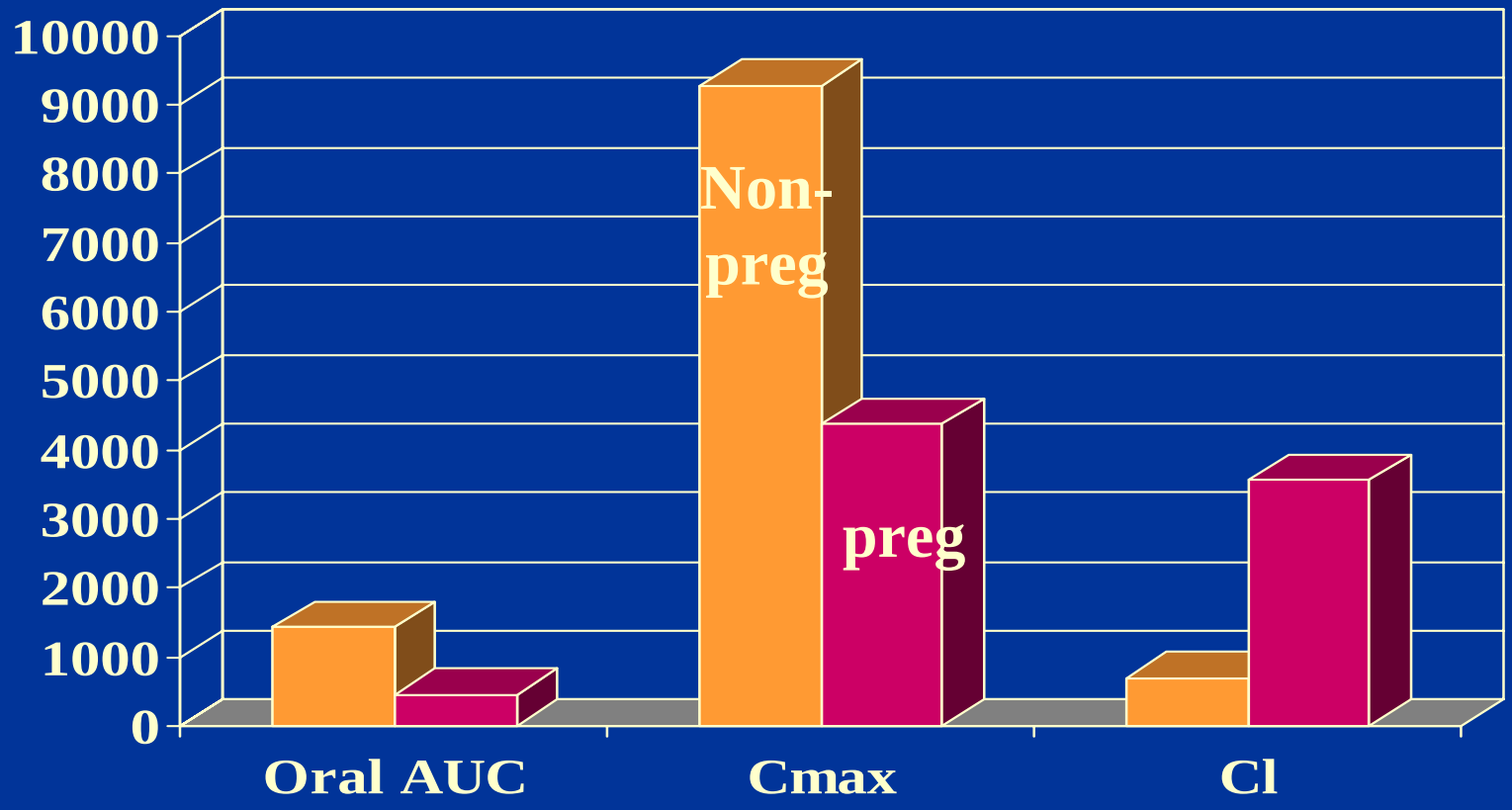
- 14-32 wk HIV-infected pregnant women (n=4 completed)

- cross study comparison (vs. non-pregnant data (n=31) --- <4-fold AUC reduction>

< Acosta EP, et al, HIV Clin Trials 2001; 2:460> <PDR for Fortovase, July 2002>

Indinavir

- 14-28 wk vs. 6 wk postpartum in HIV-infected pregnant women (n=11)



- <3-fold AUC reduction>

< Unadkat J, CDER VPLS seminar, June 13, 2003>

There appears to be upregulation of certain CYP enzymes & P-gp during pregnancy

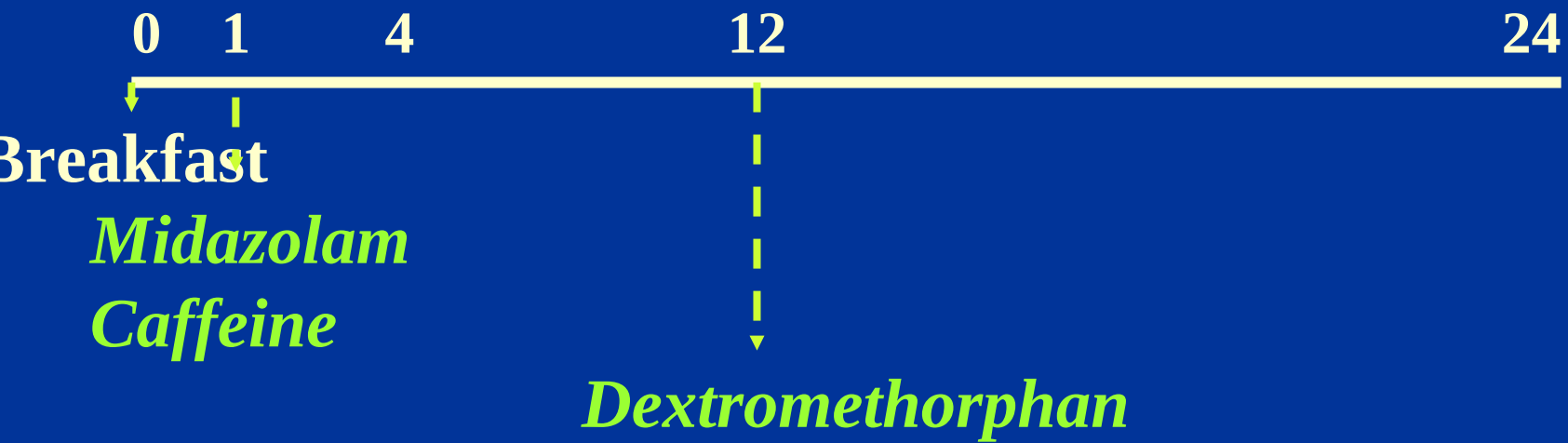
FDA/Indiana University Study

- **Cocktail approach**

  - (CYP3A, 1A2, 2D6, 2C9 probes) used in evaluation of St John's Wort or Echinacea effects on metabolizing enzymes at hepatic and intestinal sites

FDA/Indiana University Study

- **Cocktail approach**
  - **CYP3A: midazolam (5 mg)**
  - **CYP1A2: caffeine (200 mg)**
  - **CYP2D6 : dextromethorphan (30 mg)**



FDA/Indiana University Study

- **Evaluate in three periods**

  - Weeks of 20-24, 30-34, and 10-14 post-partum

---> Determine effects of pregnancy on CYP1A2, 2D6, and 3A (responsible for > 80% of metabolized drugs)

< Study design discussions:
Indiana University: Hall S, Gorski C. Lau J, Hilligoss, J, Craven R, Flockhart DA
CDER/FDA: Huang SM, Lesko L, Uhl K, Miller M, Kweder S, Chang N, Green L, Pollock M, Hixon D>

Conclusion

- It is critical to evaluate various extrinsic and intrinsic factors that affect the pharmacokinetics and -dynamics of drugs
- Quantitative tools are available and continue to be developed to evaluate exposure-response relationship
- Improved understanding and development of various in vitro and in vivo tools can aid in assessment and management of drug risks